

## CONFIDENTIAL

# Statistical Analysis Plan

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Open Label Randomized, Multi-centre Phase III Trial of TPF Plus Concomitant Treatment With Cisplatin and Radiotherapy Versus Concomitant Cetuximab and Radiotherapy in Locally Advanced, Unresectable Head and Neck Cancer.

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## ABBREVIATIONS

AE	Adverse event
AJCC	American Joint Commission for Cancer
BSA	Body surface area
CI	Confidence interval
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTC	Common toxicity criteria
DP	Disease progression
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
HNSCC	Head and Neck Squamous Cell Carcinoma
HR	Hazard ratio
IR	Incomplete response
ITT	Intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
ORR	Overall response rate
OS	Overall survival
PFS	Progression free survival
PP	Per protocol
PR	Partial response
PT	Preferred term
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event
SD	Stable disease
SOC	System organ class
TNM	Tumour-lymph node-metastasis classification
TPF	Docetaxel, cisplatin, 5-fluorouracil
UNL	Upper normal limit
WHO	World Health Organization

## 1 INTRODUCTION

Despite all the therapeutic advances in the treatment of head and neck squamous cell carcinoma (HNSCC) patients with locally unresectable advanced HNSCC continue to have a poor prognosis -18.6 months- when dealing with docetaxel, cisplatin and 5-fluorouracil (TPF) in the larger updated study<sup>i,ii,iii</sup>. The TPF regimen should be the therapeutic basis to be added to the new biological treatments and try to improve the results without significantly increasing its toxicity<sup>iv</sup>.

The association of induction chemotherapy with TPF followed by concomitant chemoradiotherapy with cisplatin appears at this time as the new standard treatment in unresectable disease. However, the chemoradiotherapy regimen should be reconsidered after induction chemotherapy. All, of course, safety and the realization that it has been achieved to improve the effectiveness of radiotherapy (RT) with the aim, as well as control of the disease and survival in the locally advanced HNSCC, however, acute toxicity and/or chronic associated with RT (Section 3.A.2.6.3 of the protocol).

For this reason, this phase III randomized study has been designed. All patients with locally unresectable advanced HNSCC initiated treatment with induction chemotherapy with the TPF scheme. Patients with progression to this chemotherapy scheme left the study because it is known that the possibility of curing these patients is practically nil, so each centre decided which was the best treatment to avoid causing excessive toxicity. Patients with a response to induction chemotherapy or stable disease (SD) were randomized to a control arm (chemoradiotherapy with cisplatin), which is considered standard by the Spanish Head and Neck Cancer Treatment Group, or they received the treatment branch which we consider experimental (RT combined with cetuximab).

The study aims to evaluate the non-inferiority of the experimental branch with respect to the standard branch in terms of overall survival (OS) in patients with a locally advanced and unresectable squamous cell carcinoma of the head and neck who have responded to an induction chemotherapy with the TPF scheme. In addition, it is intended to carefully compare the acute and chronic toxicity of both treatment branches, as well as the quality of life (QoL) of patients subject to said treatments.

## **2 STUDY OBJECTIVES**

### **Primary Objective**

To demonstrate that induction (TPF) chemotherapy followed by RT + Cetuximab is at least non-inferior to chemotherapy with TPF followed by RT + Cisplatin in terms of OS in patients with unresectable HNSCC.

### **Secondary Objective**

The secondary objectives were:

- To evaluate the activity and safety of TPF treatment.
- To evaluate the reasons for study non-continuation (possibility of complying with randomisation criteria) after induction treatment with TPF.
- To evaluate and compare efficacy in the 2 treatment groups (experimental arm versus standard arm):
  - Disease free survival
  - Specific disease survival
  - Overall survival
  - Time to locoregional control of disease
  - Time to treatment failure
- To evaluate and compare the safety activity and safety profiles of the 2 treatment groups (experimental versus standard):
  - Response rate
  - Acute and chronic toxicity rates
- To evaluate and compare the patient perceptions using QoL questionnaires.
- To evaluate the treatment compliance rate with RT plus Cetuximab and RT plus cisplatin, after combination with induction and TPF.

### 3 GLOBAL STUDY DESIGN

#### 3.1 Study design and description of the experimental plan

Phase III, open-label, randomised and multicentre clinical trial in patients with unresectable locally advanced HNSCC.

All patients will start treatment with 3 cycles of induction chemotherapy with the TPF scheme, after signing the informed consent.

1. Patients who progress to treatment with TPF will be excluded from the study and will be treated according to the protocol of each Centre.
2. Patients with toxicity to treatment with TPF that does not allow to continue with a treatment that includes cisplatin, will be excluded from the study and will be treated according to the protocol of each centre and in accordance with international recommendations.
3. Patients who have not been able to receive at least two induction cycles will be excluded from the study and will be treated according to the protocol of each centre and in accordance with international recommendations.
4. Patients with a response or stabilization to TPF who can follow a treatment that includes cisplatin will be randomized to receive normofractionated RT plus cisplatin (Group A versus the combination of cetuximab with normofractionated RT (experimental Group B).
5. Patients will be stratified according to location (oral cavity, versus oropharynx, versus larynx versus hypopharynx) to ensure a homogeneous distribution.

Therefore, there are two differentiated parts in the study:

- Part 1 of the study: the period from the signing of the informed consent form until the response and toxicity assessment of induction chemotherapy with TPF (standard group)
- Part 2 of the study: the period from randomisation following induction chemotherapy with TPF until the end of study (experimental group)

The neoadjuvant treatment will be done according to the following scheme:

#### SCHEME OF THE COMBINATION OF INDUCTION CHEMOTHERAPY

Drugs	Daily dose	Administration	Days
Docetaxel	75 mg/m <sup>2</sup> /d	IV 1 hour	1
Cisplatin	75 mg/m <sup>2</sup> /d	IV 1 hour	1
5-Fluorouracil	750 mg/m <sup>2</sup> /d	24-hour infusion	1-5
Dexamethasone	16 mg	8 mg/12 hours	-1, 1 and 2
Ciprofloxacin (or equivalent)	1 g	500 mg/12 hours	D 7-15
G-CSF*	150 µg/m <sup>2</sup> /d	SC	D 7-12

\*Lenograstim (Granocyte®) is recommended. If another granulocyte-colony stimulating factor (G-CSF) is used, it has to be administered according to the summary of product characteristics.

Patients who presented an objective response or stabilisation to the TPF treatment, who received at least 2 cycles of induction therapy and did not have any contraindications to continued cisplatin treatment, will be randomised into 2 radical treatment groups:

- **Group A** (standard): Concomitant RT with cisplatin: at 3-4 weeks (5 weeks at most) from the beginning of the 3rd TPF cycle, treatment began with concomitant normofractionated RT with chemotherapy (cisplatin 100 mg/m<sup>2</sup> IV).

Drugs	Daily dose	Administration	Days
Cisplatin	100 mg/m <sup>2</sup> /d	IV 1 hour	1, 22 and 43 of the RT

- Cisplatin will be administered every three weeks from the first day of RT.

- **Group B** (experimental): Concomitant RT with cetuximab: at 3-4 weeks (5 weeks at most) from the beginning of the 3rd TPF cycle, treatment began with normofractionated RT. Cetuximab would have started the week before.

Drugs	Daily dose	Administration	Days
Cetuximab*	250 mg/m <sup>2</sup> /d	IV 1 hour	1, 8, 15, 22, 29, 36, 43 and 50**

\*Initial dose of 400 mg/m<sup>2</sup>/day in the first infusion for 120 minutes

\*\* Or to the end of the RT if there is any delay

- Cetuximab will be administered continuously weekly, from one week before the start of RT (loading dose).



## RADIOTHERAPY SCHEME (same for branch A and branch B)

Radiotherapy	Total dose	Dose per fraction
Normofractionated	70 Gy	2 Gy per fraction 35 fractions 1 fraction a day

### Inclusion criteria

For inclusion in the study, all of the following inclusion criteria must be met:

1. Before beginning the specific procedures of the protocol, informed written consent had to be obtained and documented.
2. Locally advanced cancer of the head and neck (oral cavity, oropharynx, larynx and hypopharynx), stage III-IV, with no evidence of metastasis.
3. The tumour had to be classified as inoperable according to Northern California Oncology Group (Fu KK et al. J Clin Oncol, 1987) criteria after assessment by a multidisciplinary team, which included, at least, a specialist in oncological surgery from the Ears, Nose and Throat Department or a specialist in maxillofacial surgery (as applicable), a specialist in Medical Oncology and a specialist in Radiotherapy oncology. The reason for inoperability were recorded on the case report form (CRF).

NCOG inoperability criteria:

- Technically non-resectable (included: evidence of mediastinal dissemination; tumour fixed to the clavicle, base of the cranium or cervical vertebrae; involvement of the nasopharynx).
  - Medical criteria based on a low surgical curability.
  - Medical contraindication for surgery.
4. Anatomically and pathologically proven epidermoid carcinoma.
  5. Disease measurable according to the modified RECIST 1.0 criteria.
  6. Men or women aged 18 to 70 inclusive.
  7. ECOG performance status: 0 or 1
  8. Patients in a medical condition to be able to receive induction treatment with TPF followed by normofractionated RT with cetuximab or cisplatin.

9. Patients with adequate haematological function: neutrophils  $\geq 2 \times 10^9$ , platelets  $\geq 100 \times 10^9$ , haemoglobin  $\geq 9$  g/dL and no symptoms related to anaemia.
10. Adequate liver function: Bilirubin  $\leq 1.5 \times$  upper normal limit (UNL), and some of the following parameters: glutamic oxaloacetic transaminase (GOT)  $\leq 2.5$  UNL or alanine aminotransferase (GPT)  $\leq 2.5$  ULN or alkaline phosphatase  $< 2$  UNL; however, if all of these are present, their value should not have exceeded the UNL.
11. Adequate kidney function: serum creatinine  $< 1.4$  mg/dL ( $120 \mu\text{mol/L}$ ); if the values are  $> 1.4$  mg/dL, creatinine clearance had to be  $> 60$  mL/min (real or calculated by the Cockcroft–Gault method).
12. Adequate nutritional status: BMI  $> 18.5\%$  or albumin  $\geq 30$  g/L.
13. Patients had to be accessible for treatment and follow-up.

#### Exclusion criteria

Patients cannot be included in the study if they meet any of the following criteria:

1. Metastatic disease
2. Previous treatment by surgery, with RT and/or chemotherapy for the disease being studied.
3. Other tumour locations in the head and neck area, other than the oral cavity, oropharynx, larynx and hypopharynx.
4. Stages other than stage III or IVM0.
5. A previous and/or synchronous squamous carcinoma.
6. Diagnosis of another neoplasia in the past 5 years except properly treated cervical carcinoma *in situ* and/or basal cell carcinoma.
7. Active infection (infection that required intravenous antibiotics), including diagnosed active tuberculosis and HIV.
8. Uncontrolled hypertension defined as systolic blood pressure  $\geq 180$  mm Hg and/or diastolic blood pressure  $\geq 130$  mm Hg at rest.
9. Pregnancy (its absence should be confirmed by a serum  $\beta$ -HCG test) or lactation.
10. Systemic, chronic and concomitant immune therapy or hormone therapy for cancer.

11. Other concomitant antineoplastic treatments.
12. Clinically significant coronary artery disease or a history of myocardial infarction in the past 12 months or high risk of uncontrolled arrhythmia or uncontrolled heart failure.
13. Chronic obstructive pulmonary disease that required  $\geq 3$  hospitalisations in the previous 12 months.
14. Uncontrolled active peptic ulcer.
15. Presence of a psychological or medical illness that would prevent the patient from taking part in the study or from granting informed consent.
16. Known drug abuse (except for heavy drinking).
17. Known allergic reaction to any of the ingredients of the study treatment.
18. Previous treatment with monoclonal antibodies or other inhibitors of signal transduction or epidermal growth factor receptor (EGFR) inhibitors.
19. Any experimental treatment in the 30 days prior to study entry.

### 3.2 Sample size

The objective of the trial will be to demonstrate the non-inferiority of the experimental arm compared to the standard arm in terms of OS, using time to death due to any cause as the primary endpoint.

In the analysis of OS, which is the primary endpoint proposed in this study, the Cox proportional hazards regression will be used. The general formula of the hypothesis to at least prove non-inferiority will be as follows:

$$H_0: HR_{\text{Experimental Arm / Standard Arm}} \geq 1.3$$

$$H_1: HR_{\text{Experimental Arm / Standard Arm}} < 1.3$$

Calculation of sample size is based on an assumed exponential distribution, using the following parameters:

- Unilateral testing with an alpha of 0.05 and 80% power.
- A recruitment phase of 53 months.
- A follow-up phase of 36 months.
- A hazard ratio (HR) of 0.0231 for the standard arm (median progression-free survival (PFS) of 30 months)
- $HR_{\text{Experimental arms/Standard arms}} = 0.938$  (this assumes a median of 32 months for the experimental arm)
- Competing risk of 0.01.

The total number of randomised and evaluable patients is 398. At this size, we also have to add 15% of the patients who will progress with TPF or will be lost (dropouts or TPF toxicity that provide continued cisplatin administration), so the patient total will be 469.

## **4 EFFICACY AND SAFETY ENDPOINTS**

### **4.1 Primary efficacy endpoint**

The study's primary endpoint is OS defined as time between the start of treatment with TPF and death due to any cause.

### **4.2 Secondary efficacy endpoints**

The secondary endpoints of the study are:

- Overall response rate (ORR) (according to the modified RECIST 1.0 criteria), will be measured for induction chemotherapy and also for both radical treatment arms after TPF (RT + Cisplatin and RT + Cetuximab)
- PFS
- Specific survival.
- Time to locoregional control of disease
- Satisfaction with treatment. Analysis of QoL in both treatment arms.

### **4.3 Safety endpoints**

The study's safety endpoint are:

- Incidence of adverse events (AEs) and serious adverse events (SAEs) (clinical and laboratory parameters)
- Early withdrawals from the study
- Incidence and time when dose reductions or suspensions are carried out (rate of compliance with the protocol in both treatment arms)

## 5 ANALYSIS POPULATIONS

The assignment of the patients to any of the populations mentioned below will be made before closing the database.

The analysis populations will be defined according to the part of the study:

*Part 1 of the study* (period from the signing of the informed consent form until the evolution of response and toxicity to induction chemotherapy with TPF)

- A. **Safety population 1:** all patients who have signed the informed consent form and who have received at least one dose of chemotherapy with TPF.
- B. **Intention-to-treat population 1:** all patients enrolled who have received at least one dose of TPF chemotherapy.

*Part 2 of the study* (period from randomisation after TPF chemotherapy and until the end of study)

- C. **Safety population 2:** all randomised patients who have initiated the assigned radical treatment.
- D. **Intention-to-treat population 2:** all randomised patients who have at least begun their assigned radical treatment.

## 6 STATISTICAL METHODS

The titles of the tables and listings planned for the analysis are shown in appendix I.

### 6.1 Changes in the planned statistical analysis

Any change in the analysis defined in this statistical analysis plan once it has been finalized and the databases have been closed (database lock), will be detailed in the clinical report.

### 6.2 Blind review

Not applicable.

### 6.3 Hypothesis and statistical methods

#### 6.3.1 Definitions

##### Age (years)

The value of age will be obtained by the following formula:

$$\text{Age} = (\text{Date of baseline visit} - \text{Birth date} + 1) / 365.25$$

##### Accumulated dose (mg/m<sup>2</sup>)

The accumulated dose per patient in a given period is the sum of the total dose levels that the patient has received within this period.

##### Docetaxel dose intensity (mg/m<sup>2</sup>/3 weeks)

Patients will receive Docetaxel doses of 75 mg/m<sup>2</sup> every three weeks. The dose intensity per patient from the first infusion is defined as:

$$\frac{\sum_{i=1}^3 \text{Cumulative dose in week } i}{\text{Date last dose week } i - \text{Date first dose week } i + 21}$$

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##### Docetaxel relative dose intensity

The relative dose intensity of Docetaxel is defined as the dose intensity divided by the planned dose:

$$\frac{\text{Dose intensity}}{75 \text{ mg/m}^2}$$

#### Cisplatin intensity dose in induction (mg/m<sup>2</sup>/3 weeks)

Patients will receive Cisplatin doses of 75 mg/m<sup>2</sup> every three weeks. The dose intensity per patient from the first infusion is defined as:

$$\frac{\sum_{i=1}^3 \frac{\text{Cumulative dose in week } i}{(\text{Date last dose week } i - \text{Date first dose week } i + 21)}}{21}$$

#### Cisplatin relative dose intensity

The relative dose intensity of Cisplatin is defined as the dose intensity divided by the planned dose:

$$\frac{\text{Dose intensity}}{75 \text{ mg/m}^2}$$

#### 5-Fluorouracil dose intensity (mg/m<sup>2</sup>/3 weeks)

Patients will receive 5-Fluorouracil doses of 750 mg/m<sup>2</sup> for 5 days every three weeks. The dose intensity per patient from the first infusion is defined as:

$$\frac{\sum_{i=1}^3 \frac{\text{Cumulative dose in week } i}{(\text{Date last dose week } i - \text{Date first dose week } i + 16)}}{21}$$

#### 5-Fluorouracil relative dose intensity

The relative dose intensity of 5-Fluorouracil is defined as the dose intensity divided by the planned dose:

$$\frac{\text{Dose intensity}}{750 \text{ mg/m}^2}$$

#### Dexamethasone dose intensity (mg/3 weeks)

Patients will receive Dexamethasone doses of 16 mg days -1, 1 and 2 of each cycle every three weeks. The dose intensity per patient from the first infusion is defined as:

$$\frac{\sum_{i=1}^3 \frac{\text{Cumulative dose in week } i}{(\text{Date last dose week } i - \text{Date first dose week } i + 19)}}{22}$$



#### Dexamethasone relative dose intensity

The relative dose intensity of Dexamethasone is defined as the dose intensity divided by the planned dose:

$$\frac{\text{Dose intensity}}{16 \text{ mg}}$$

#### Ciprofloxacin dose intensity (g/3 weeks)

Patients will receive Ciprofloxacin doses or equivalent of 1 g for 9 days (from day 7 to 15) of each cycle every three weeks. The dose intensity per patient from the first infusion is defined as:

$$\frac{\sum_{i=1}^3 \frac{\text{Cumulative dose in week } i}{(\text{Date last dose week } i - \text{Date first dose week } i + 12)}}{21}$$

#### Ciprofloxacin relative dose intensity

The relative dose intensity of Ciprofloxacin is defined as the dose intensity divided by the planned dose:

$$\frac{\text{Dose intensity}}{1 \text{ g}}$$

#### G-CSF intensity dose (g/3 weeks)

Patients will receive G-CSF doses of 150 µg/m<sup>2</sup> for 6 days (from day 7 to 12) of each cycle every three weeks. The dose intensity per patient from the first infusion is defined as:

$$\frac{\sum_{i=1}^3 \frac{\text{Cumulative dose in week } i}{(\text{Date last dose week } i - \text{Date first dose week } i + 15)}}{21}$$

#### G-CSF relative dose intensity

The relative dose intensity of G-CSF is defined as the dose intensity divided by the planned dose:

$$\frac{\text{Dose intensity}}{150 \text{ µg/m}^2}$$

#### Group A Cisplatin dose intensity (mg/m<sup>2</sup>/3 weeks)

Patients included in Group A will receive an initial Cisplatin dose of mg/m<sup>2</sup> every three weeks. The dose intensity per patient from the second infusion is defined as:

$$\frac{\sum_{i=1}^3 \frac{\text{Cumulative dose in week } i}{(\text{Date last dose week } i - \text{Date first dose week } i + 21)}}{21}$$

#### Group A Cisplatin relative dose intensity

The relative dose intensity of Cisplatin for patients included in Group A is defined as the dose intensity divided by the planned dose:

$$\frac{\text{Dose intensity}}{250 \text{ mg/m}^2}$$

#### Cetuximab dose intensity (mg/m<sup>2</sup>/week)

Patients will receive an initial Cetuximab dose of 400 mg/m<sup>2</sup> and will continue with doses of 250 mg/m<sup>2</sup> per week. The dose intensity per patient from the second infusion is defined as:

$$\frac{\text{Accumulated dose since 1st infusion} - \text{Initial dose}}{(\text{Date last dose} - \text{Date second weekly dose} + 7)/7}$$

#### Cetuximab relative dose intensity

The relative dose intensity of Cetuximab from the second infusion is defined as the dose intensity divided by the planned dose:

$$\frac{\text{Dose intensity}}{250 \text{ mg/m}^2}$$

#### Radiotherapy dose intensity (Gy)

Patients will receive RT doses in a normofractionated form of 2 GY per fraction, 35 fractions and 1 fraction per day. They will receive a total of 70 Gy for 7 weeks. The dose intensity is defined as:

$$\frac{\text{Accumulated dose since 1st infusion}}{(\text{Date last dose} - \text{Date first weekly dose})/46}$$

#### Radiotherapy relative dose intensity

The relative dose intensity of RT is defined as the dose intensity divided by the planned dose:

*Dose intensity*  
*70 Gy*

Time calculations

Differences between dates to express duration or "time to" will be calculated as final date - start date+1. To convert these differences of days to other units, the following conversion factors will be used: 1 year = 365.25 days and 1 month = 30.4375 days.

Prognostic factors

Prognostic factors will be sex, age, location, staging and final TNM.

Duration of hospitalizations for adverse events

Difference between the start and end date of the events that have a criterion of severity of AE "Hospitalization/Prolongation" (final date - start date+1) will be calculated, and in case that the patient has several AEs with Hospitalization/Prolongation the maximum day will be selected. This difference will not be calculated when some of the dates are missing.

**6.3.2 Summary statistics**

Continuous variables will be summarised using descriptive statistics, i.e. the mean, median, standard deviation, minimum, and maximum and two-sided 95% confidence intervals (CI), when appropriate. The qualitative variables will be summarised using counts, percentages, and 95% two-sided CI, when appropriate. The differences between means or percentages will be accompanied by 95% two-sided CI or will be compared using the corresponding statistical test.

**6.3.3 Demographic data and baseline characteristics**

Demographic data and baseline characteristics will be summarized in tables for intention to treat (ITT)<sup>1</sup> and ITT<sup>2</sup>.

Patient's disposition

The allocation of the populations and the discontinuation reasons will be shown in tables. Exclusion reasons will be listed.

Demographic characteristics

Demographic variables will be described: age, sex and race.

Functional status according to ECOG

The functional status according to ECOG of the baseline visit will be tabulated by frequencies.

#### Diagnosis of the primary tumour

The data will be tabulated by frequencies according to squamous cell carcinoma grade, location, AJCC 6th edition, final tumour-lymph node-metastasis classification (TNM) and time from diagnosis until the date of the baseline visit.

#### Complete physical examination and direct optical examination of the head and neck area

The location of the primary lesion will be tabulated using a table of frequencies.

Similarly, optical tumour exploration (including the maximum diameter of the lesion) will be described.

#### Physical exploration

The variables height, weight and area of the body surface (BSA) will be described.

On the other hand, the number of patients that have shown abnormalities in the different devices and systems examined will be described: cardiovascular, respiratory, nervous, gastrointestinal, lymphatic, genitourinary, dermatological, musculoskeletal, extremities and eyes.

#### Dental evaluation

The number of patients who have shown abnormalities in the dental evaluation will be described.

#### Relevant clinical history

The relevant diagnoses and diseases will be described by the number of affected patients and the percentage of the total number of patients.

#### Electrocardiogram

The number of patients who have shown abnormalities on the electrocardiogram will be described.

#### Thorax radiography

The number of patients who have shown abnormalities on the chest radiograph will be described.

#### Gammagraphy

The number of patients who have shown abnormalities on the gammagraphy will be described.

#### Nutritional evaluation of the patient

The nutritional assessment of the patient will be tabulated using a table of frequencies.

#### Radiological studies by computed tomography (CT) or magnetic resonance imaging (MRI)

In this section, the number of target and non-target lesions evaluated with a radiological study by CT or MRI at the baseline visit will be shown.

#### **6.3.4 Primary efficacy analysis: overall survival**

OS is defined as: the time from the start of induction chemotherapy with TPF to death due to any cause or to the last check-up in the case of living patients.

The study's primary analysis will be performed on the ITT population that was randomised into the standard arm or the experimental arm. It will be tested using the following hypotheses, if the experimental treatment group is, at least, non-inferior to the standard group:

H0: Hazard ratio  $\text{Experimental arm / Standard arm} \geq 1.3$ .

H1: Hazard ratio  $\text{Experimental arm / Standard arm} < 1.3$

The one-sided alpha level specified in the study protocol is 0.05. Thus, non-inferiority can be concluded if the upper limit of the two-sided 90% CI for the HR is below 1.3.

#### **6.3.5 Analysis of the secondary objectives**

##### Overall Survival

OS is defined as: the time from the start of induction chemotherapy with TPF to death due to any cause or to the last check-up in the case of living patients.

The analysis will be performed on the ITT population of part 2 and ITT of part 1.

The results of a proportional hazards regression model, which include the factors used for stratification and/or prognostic factors in this disease, will be also presented in the ITT populations, in order to evaluate the sensitivity of the main analysis.

In addition to the risk reasons and their corresponding one-sided 95% CIs, the results of these analyses were summarised for each treatment group, with data in the form of Kaplan-Meier graphs and median survival rates at 2, 3 and 5 years, with the corresponding 95% unilateral CI.

##### Response evaluation

The overall response is defined according to the assessments of the target and non-target lesions, taking into account also the appearance of new lesions. The definition are:

a) Evaluation of the target lesions

Complete response (CR)	Disappearance of all target lesions.
Partial response (PR)	Reduction of at least 30% in the sum of the largest diameter of all target lesions taking as a reference the sum of the largest diameters at baseline.
Stable disease (SD)	There is neither sufficient reduction to classify it as PR nor sufficient increase to classify it as DP; in other words, a decrease in the sum of the greatest diameter of all target lesions less than 30%, taking the baseline measurement as the reference or an increase of this diameter by less than 20%, using the smallest sum of larger diameters after the start of treatment as the reference.
Disease progression (DP)	An increase of 20% or more of the sum of the largest diameter of all target lesions, using the smallest sum of larger diameters since the treatment started as the reference.

b) Evaluation of non-target lesions:

Complete response (CR)	Disappearance of all non-target lesions.
Incomplete response (IR) /stable disease (SD)	Persistence of one or more non-target lesions.
Disease progression (DP)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. (Although a clear progression of non-target lesions is exceptional, in these circumstances, the physician's opinion must prevail).

Patients with a global deterioration in their health that require discontinuation of treatment without objective evidence of DP at that time will be classified as "symptomatic deterioration". Every effort have to be made to document progression even after discontinuing treatment.

The overall response will be obtained from the values taken from the target and non-target lesions, and taking into account the appearance or lack thereof of new lesions. Following table shows all overall responses of potential combinations of tumour responses. The overall response assessments will be carried out on each visit in which a response evaluation has been scheduled.

c) Assessment of overall response

Target lesions:	Non-target lesions.	New lesions	Overall response
CR	CR	No	CR
CR	IR/SD <sub>1</sub>	No	PR
PR	No-DP	No	PR
SD	No-DP	No	SD
DP	Any	Yes or no	DP
Any	DP	Yes or no	DP
Any	Any	Yes	DP

### Overall response rate

The ORR is defined as the response rate (CR + PR) measured using the RECIST 1.0 method.

The populations analysed are: in part 1 after induction therapy, ITT population, and in part 2, also the ITT per protocol (PP) population.

The results on part 1 will be presented in absolute and relative frequency tables and the corresponding 95% CI.

The results from part 2, as well as the absolute and relative frequency tables with a 95% CI for each treatment group, the response rates will be compared using the chi-squared test (or the corresponding non-parametric test) with a 95% CI.

Using the ITT population 1, exploratory analyses will be performed to search for prognostic factors in the response rate.

### Adverse events rate and laboratory parameters

All the AEs that appeared were recorded in the CRF were recorded according to the following criteria:

1. NCI CTC, version 3.0 during the induction treatment (see Protocol, Appendix 3).
2. NCI CTC, version 3.0 (see Protocol, Appendix 3) and CTC of the RTOG during Chemotherapy/RT or Cetuximab/RT and 90 days after completion of the RT (see Protocol, Appendix 4). In case of doubt, the criteria that assessed the AE to be the highest grade will be used.
3. Late CTC from the RTOG/EORTC from 90 days after completion of RT, which will be basically used to gather chronic toxicity associated with radio-chemotherapy (see Protocol, Appendix 5)

AEs will be presented in the form of lists and summarised by absolute and relative frequency tables. A table for part 1 (induction therapy) and another for the part 2 treatment assigned by the randomisation group will be presented. In both the AEs will be separated according to whether they are related to the study medication or not. When classification of the relationship with the study medication will be lacking, it will be deemed to be related to the study medication.

Laboratory data will be presented by the incidence of toxicities according to the corresponding criteria and changes from the baseline to the highest degree of toxicity, according to the given criteria, as described during treatment.

All abstracts and lists of AEs and laboratory data will be based on the safety population.

Part 2 of the study will compare the grade 3 and 4 AEs and laboratory data in each of the treatment arms using a 95% CI of the differences in rates.

### Vital Signs

Vital signs values (blood pressure, heart rate and body temperature) will be described for visit 1 using descriptive statistics.

### Early withdrawals from the study

The main reason for withdrawal from the study will be recorded in the case report form. Lists and summary tables will be provided, giving the reason for the end of the study and when it occurred.

These summaries and lists will be based on the safety population. Part 2 of the study will be separated by assigned treatment arm.

### Incidence and time when dose reductions or suspensions will be carried out

Details and summary tables will be provided, providing the incidence of reductions or treatment discontinuations and giving the reason.

These summaries and lists will be based on the safety population. Part 2 of the study will be separated by assigned treatment arm.

### Progression-free survival

For the PFS analysis, we define time to progression as the time since the start date of treatment with TPF induction chemotherapy until the time when DP occurred or death occurred due to any cause. Patients who show no progression or die will be censored on the date of the last check-up. Patients for whom no tumour assessments will be available after the baseline evaluation will be censored on day 1. Patients who show no progression and



begin a cancer treatment other than that of the study will be censored on the start date of the other treatment.

This analysis will be performed on the ITT populations in both parts of the study.

In part 2, the study has no power to show statistical differences or equivalences between the two treatment groups after randomisation. Using the Cox proportional hazards regression, the risk ratio will be presented together with its 95% CI, as well as the Kaplan-Meier estimations of the survival curves for each treatment group (including survival rates and medians at 2, 3 and 5 years, with their corresponding 95% CI). The regression model also will include the factors used for stratification and/or prognostic factors of this disease in order to assess the robustness of the primary analysis.

#### Disease-free specific survival

For the disease-specific survival analysis, we define TTP as time elapsed from the start date of treatment with TPF induction chemotherapy to date of death due to disease or related to the treatment of the disease. Deaths caused by other reasons will be considered "censored" data on the date of death. Patients who die will be censored on the date of the last check-up.

This analysis will be performed on the ITT populations in both parts of the study. In part 2, the study has no power to show statistical differences or equivalences between the two treatment groups after randomisation. Using the Cox proportional hazards regression, the risk ratio will be presented together with its 95% CI, as well as the Kaplan-Meier estimations of the survival curves for each treatment group (including survival rates and medians at 2, 3 and 5 years, with their corresponding 95% CI). The regression model will also include the factors used for stratification and/or prognostic factors of this disease in order to assess the robustness of the primary analysis.

#### Time to locoregional control of disease

Locoregional control: is defined as permanent and complete resolution of the disease in terms of its initial site and lymph nodes (T and N). If the disease lasted (regardless of size), the tumour recurred, or a second tumour appeared in the field RT, it will be recorded as a therapeutic failure. This will allow for surgical rescue on the lymph nodes if after the evaluation at the end of RT the cervical adenopathy remain but the primary tumour will be under control (indicated as part of the first treatment). Locoregional failure is considered in

cases of patients who has rescue surgery on the primary tumour (T surgery) because of its persistence. Lymph node recurrence after a complete cervical lymph node remission will also be considered a therapeutic failure. In some cases, residual tumours may persist, consisting of areas of fibrosis or scarring, which may remain stable or resolve gradually over time and which are not accompanied by evidence of locoregional disease progression or clinical deterioration.

We define disease locoregional control time as time from the start of TPF induction chemotherapy to tumour recurrence or the appearance of a second tumour within the RT field. Patients who do not achieve complete remission at any of the points of the analysis will be considered therapeutic failures from day 1 (start of TPF chemotherapy).

This analysis will be performed on the ITT populations in both parts of the study.

In part 2, the study has no power to show statistical differences or equivalences between the two treatment groups after randomisation. Using the Cox proportional hazards regression, the risk ratio will be presented together with its 95% CI, as well as the Kaplan-Meier estimations of the survival curves for each treatment group (including and survival rates and medians at 2, 3 and 5 years, with their corresponding 95% CI). The regression model will also include the factors used for stratification and/or prognostic factors of this disease in order to assess the robustness of the primary analysis.

#### Time to treatment failure

The time to failure of treatment is the time elapsed between the start of induction chemotherapy with TPF until the decision to terminate treatment for any reason. For the subjects who remain in the treatment phase at the time of the analysis, the time to treatment failure will be recorded on the date of their last evaluation during the study. This analysis will be performed on the ITT populations in both parts of the study.

In part 2, the study has no power to show differences or statistical equivalences between the two groups of treatments after randomization. Using the Cox proportional hazards regression, the risk ratio will be presented along with its 95% CI, in addition to the Kaplan-Meier estimates of the survival curves of each treatment group (including the median and survival rates at 2, 3 and 5 years, with corresponding 95% CI). The regression model will also include the factors used for the stratification and/or prognostic factors of this disease, in order to assess the robustness of the main analysis.

### Satisfaction with treatment. Quality-of-life analysis in both treatment arms

EORTC QoL questionnaires is chose for this study. QLQ-C30 version 3.0 (1), which is a basic questionnaire with 30 items and the QLQ-H&N35 module (2), which is made up of 35 items.

These questionnaires will be self-completed by the patients when they will be in the site. They will have to complete them before starting TPF induction chemotherapy, after 3 cycles of TPF, just before the patient know the radical treatment arm to which they have been assigned, and then 6-8 weeks after completion of RT and every 6 months during the follow-up visits for the first and second year. If the time for completing the questionnaire coincide with an assessment of the tumour, the patient will fill it in before knowing the results of the tumour study.

Overall scores and those per field in the total population and per treatment group will be described. A comparative analysis will be performed on the different scales according to the treatment assigned by the randomisation. The QoL population (patients who complete the questionnaires) that is explained in section 12.C (see Protocol) will be used for these analyses.

#### **6.3.6 Exposure to the study drug**

Lists and summary tables indicating the incidence of reductions or suspensions of treatment indicating the reason will also be provided.

#### **6.3.7 Concomitant medication**

All concomitant medications taken during the course of the study will be recorded in the CRF and will be coded using the WHO Drug Dictionary. Such medications will be described by the number of patients affected and the percentage of the total number of patients.

#### **6.3.8 Adverse events**

AEs recorded after the start of treatment with Panitumumab will be coded using the MedDRA medical dictionary and will be classified according to version 3.0 of the Common Toxicity Criteria (CTC) of the National Cancer Institute (NCI).

The number and percentage of patients who experienced some AE will be tabulated by:

- System Organ Class (SOC) and preferred term (PT).
- SOC, PT and relation to the study medication.

- SOC, PT and degree of severity.
- SOC, PT and severity.

AEs that are reported as having a relationship with the study medication "possible", "probable" or "safe/definitive" will be considered related to study medication. When the classification regarding the relationship with the study medication is missing, it will be considered related to the study medication.

The frequencies of the AEs related to the medication will also be calculated.

Similarly, the number and percentage of patients who experienced a severe AE will be tabulated by:

- SOC and PT.
- SOC, PT and degree of severity.
- SOC, PT and relationship with the study medication.

The incidence of grade III and IV toxicities will be described according to the grouping of adverse events described in Appendix 3 by SOC and PT in the TPF period. The incidence of grade II, III and IV toxicities will be described according to the grouping of AEs described in Appendix 3 by SOC and PT in the RT period + Cetuximab or RT + Cisplatin.

*A toxicity will be considered to belong to a given period when the date of onset of the toxin is between the start date and the end date of the treatment administrations of the period.*

Finally, a list of AE patients will be generated showing the details collected in the data collection notebook.

### **6.3.9 Other security variables**

#### Laboratory parameters

The individual laboratory parameters (haematology and biochemistry) for both ITT1 and ITT2 population will be analysed descriptively by visit, both for the values observed and for the changes with respect to the baseline visit.

Similarly, they will be presented through the incidences of toxicities according to the corresponding criteria and the changes from the baseline to the highest degree of toxicity described during the treatment.

Frequencies of the pregnancy test that should be performed on women with the possibility of pregnancy will be shown.

#### Functional status according to ECOG

The functional status data according to ECOG will be analysed descriptively by visit (*including the ECOG evaluated before the start of TPP and prior to the treatment of group A / B*), both for the observed values and for the changes with respect to the baseline visit.

#### Dental evaluation

The data of the dental evaluation of the patient at the baseline visit will be analysed using frequencies.

#### Locoregional evaluation

The data of the therapeutic failure will be analysed descriptively.

#### Cervical lymph node dissection

The data from cervical ganglion dissection will be analysed descriptively by visit.

#### Detailed exploration of the head and neck area

The location of the primary lesion will be tabulated using a table of frequencies. Similarly, cervical adenopathies will be described.

#### Delayed toxicity

The toxicity data will be analysed using a table of frequencies per visit.

#### Other antineoplastic treatments

The data of the antineoplastic treatments after the end of the study will be analysed descriptively.

### Patient's status

The states of the patients will be differentiated in:

- VSE: alive without disease
- VCE: alive with illness. Patients who have progressed.
- Exitus

At the end of the induction period with TPF (part 1 of the study), at the end of the concomitant RT with cisplatin/cetuximab (part 2 of the study) and at the last follow-up after progression.

### **6.4 Level of significance, multiple comparisons and multiplicity**

The level of significance used for the confidence intervals will be 0.05 in tests of bilateral hypotheses.

No multiple comparisons or multiplicity cases are expected in this study.

### **6.5 Adjustments for covariates**

In this study, adjustment for covariates is not expected.

### **6.6 Handling of dropouts and missing data**

If date is incomplete after the Data Management process and this date should be used to perform some calculation (i.e. 'age'), the following assignment will be made in the missing data:

- if no field is available: no imputation will be made
- if only the year is available: the day "01" and the month of "July" will be charged
- if the month and the year are available: the day "15" will be imputed

### **6.7 Multicentric study**

No differentiate by centre analysis has been planned.

### **6.8 Subgroup analysis**

Not applicable.

## 6.9 Intermediate analyses

Two intermediate analyses are scheduled for this study: a first analysis where the safety of patients is mainly studied and a second analysis where a first review of the main efficacy analyses will be made and the safety of the treatment will also be observed.

A review committee will perform periodic analyses to monitor the safety of both treatment branches and the evaluability of the patients included.

### 6.9.1 Intermediate security analysis

An intermediate security analysis will be performed using the data from the clinical section of April 1, 2014 for the security population, and whose tables will be presented as follows:

	Tables	Listings	Graphics
Demographic data	14.1.2, 14.1.6 to 14.1.8, 14.1.10	-	-
Efficacy data	-	-	-
Safety data	14.3.41, 14.3.44 to 14.3.59 and 14.3.92	16.2.1.2, 16.2.7.1 to 16.2.7.3	-

### 6.9.2 Intermediate efficacy analysis for ASCO 2016

A second intermediate analysis will be carried out using the data from the clinical section of March 18, 2016 for ITT populations, and the tables that will be presented are the following:

	Tables	Listings	Graphics
Demographic data	14.1.2, 14.1.7, 14.1.8, 14.1.9, 14.1.10 and 14.1.11	-	-
Efficacy data	14.2.1, 14.2.2, 14.2.4, 14.2.5, 14.2.6 and 14.2.7	-	-
Safety data	14.3.9, 14.3.10, 14.3.11, 14.3.12, 14.3.16, 14.3.17, 14.3.27, 14.3.53, 14.3.56, 14.3.61, 14.3.62, 14.3.70, 14.3.86, 14.3.87, 14.3.88, 14.3.93, 14.3.94, 14.3.98, 14.3.105, 14.3.106 and 14.3.107	16.2.1.1, 16.2.1.2, 16.2.3.1, 16.2.7.2, 16.2.7.3, 16.2.7.4 and 16.2.7.8	-

## **6.10 Monitoring**

Patients will be followed and monitored periodically until death or loss of follow-up.



## 7 REFERENCES

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- <sup>iv</sup> Bernier J, Coens C, Remenar E, et al. Impact on quality of life (QoL) of the addition of docetaxel (T) to neoadjuvant cispaltin plus 5-fluorouracil treatment in patients with locally advanced unresectable squamous cell carcinoma of the head nad neck (SCCHN): an EORTC study 24971. Proc Am Soc Clin Oncol 2006; 24; 285s (A5522).